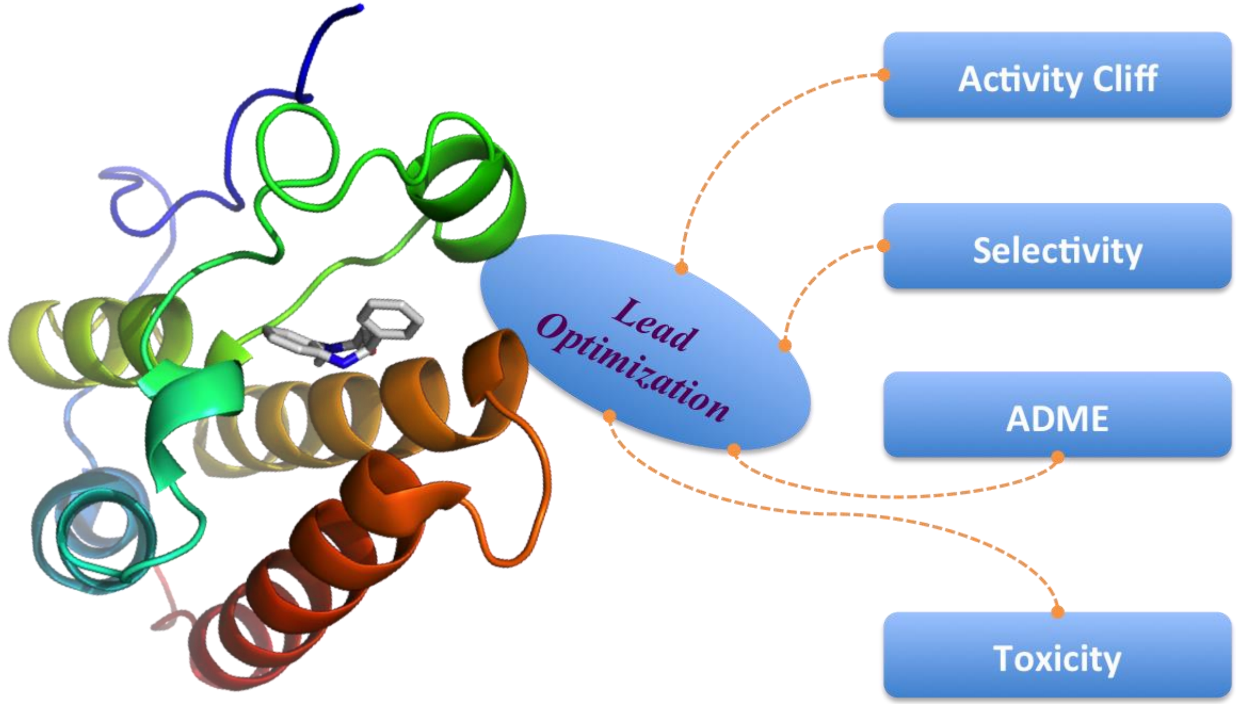


Drug Design

by

Dr. Ashraf Kareem El-Damasy

Molecular Modification of Prototype

- **Aims of designing new drugs**
  1. **Improve the activity of the lead compound.**
  2. **Improve the pharmacokinetic properties.**
  3. **Improve stability.**
  4. **Introduce new application or administration.**
  5. **Enhance selectivity between different targets.**
  6. **Reduce side effects of new drugs .**
  7. **Reduce toxicity.**
  8. **Reduce cost of production.**

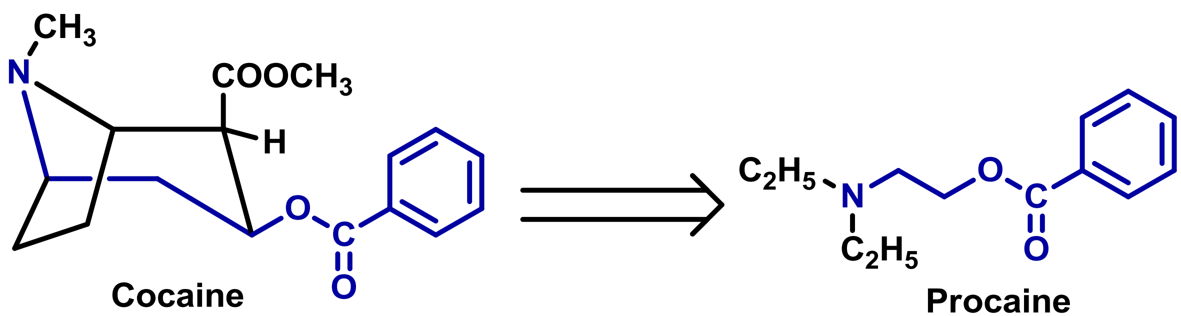
- **This process can be achieved by applying one or more of the following strategies:**
  1. **Bond disconnection and design of fragments of the lead.**
  2. **Molecular association and design of rigid analogs.**
  3. **Skeletal variation (Changing size and shape).**

1-Bond disconnection and design of fragments of the lead

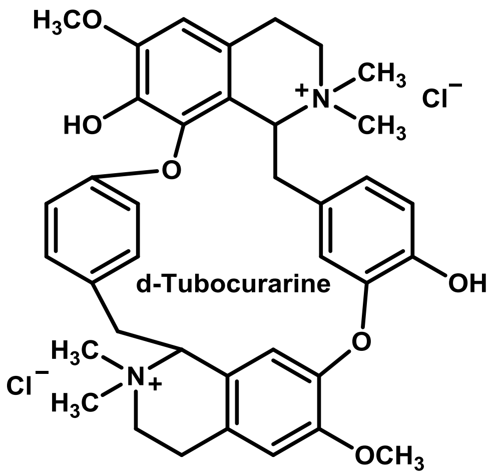
- It is the molecular simplification of a lead compound, especially the polycyclic natural products.
- It is the dissection or disjunction or trimming or dissociation of the structure.
- Molecular simplification involves cutting away sections of the molecule to determine what parts are essential and which are extra and hence:-

  Synthesis and evaluation of simpler analogs of the lead compound.

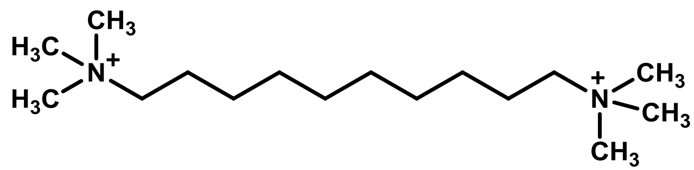
  Identifying the essential pharmacophore.
- The alkaloid cocaine is well known that it has local anesthetic properties: A simpler active analogue is procaine (Structural simplification)



1-Bond disconnection and design of fragments of the lead

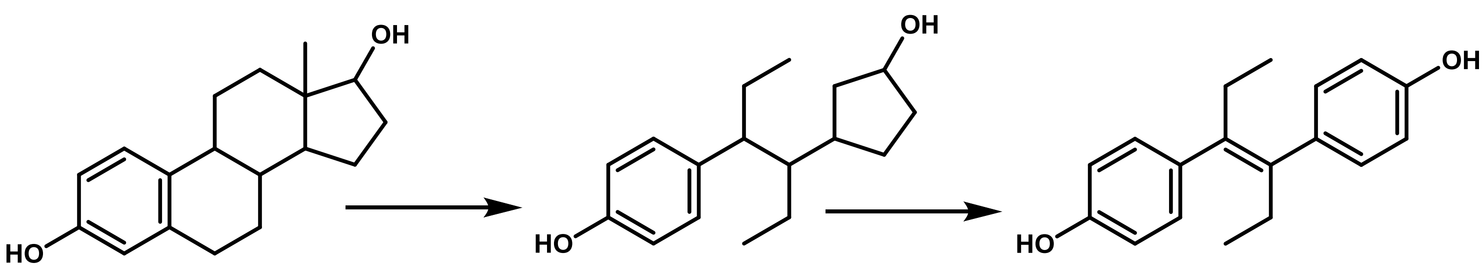


d-Tubocurarine



Decamethonium

Depolarizing muscle relaxant or neuromuscular blocking agent,
used in anesthesia to induce paralysis.

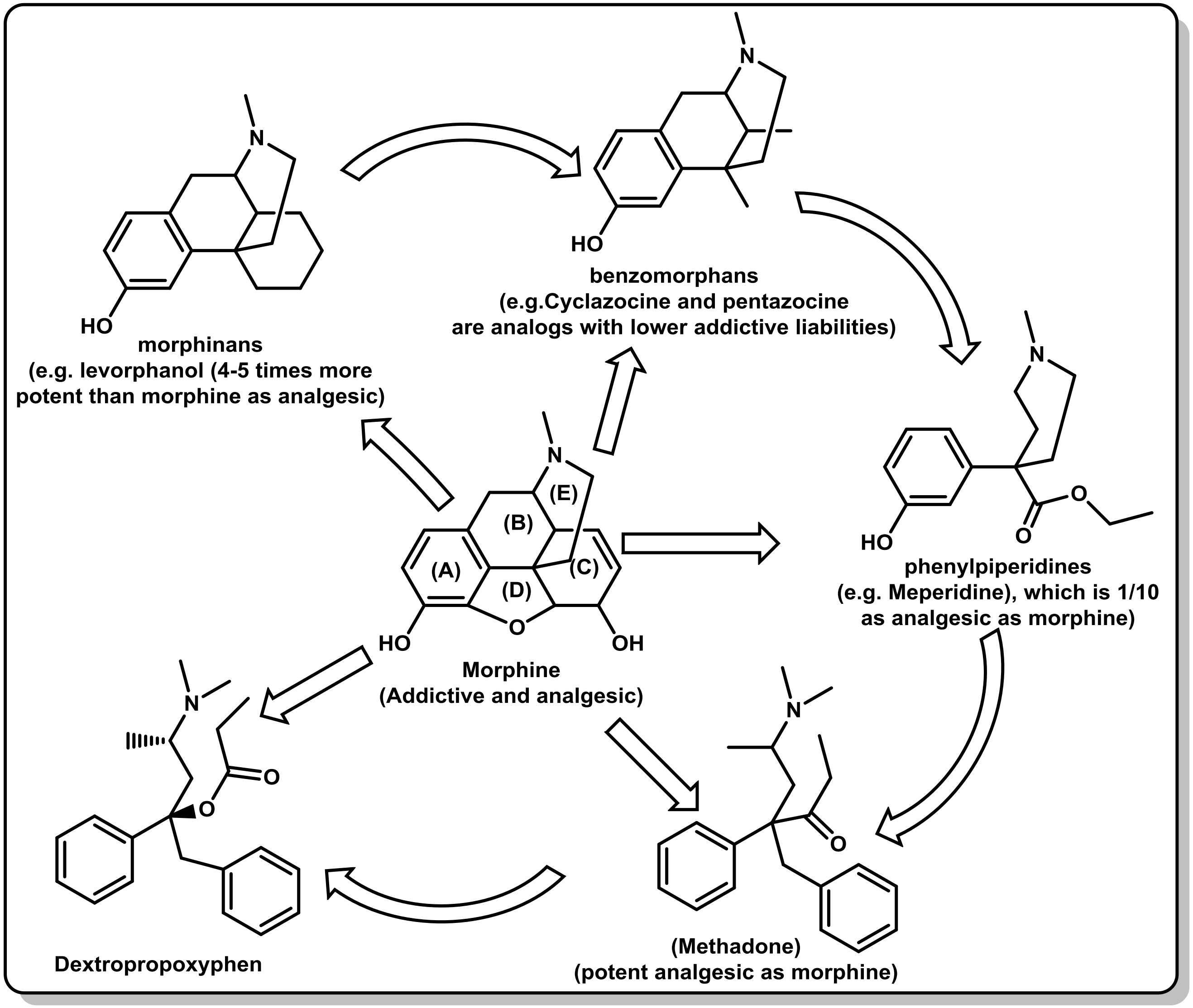


Estradiol

Diethylstilbestrol (DES)

1-Bond disconnection and design of fragments of the lead

- **Another examples of molecular simplification of a lead compound**



2-Molecular association (Conjunction)

- **The process of molecular association intends the synthesis and evaluation of more complexed analogs of the prototype.**
- **These analogs incorporate certain or all features of the lead compound.**
- **Three main types of molecular association can be distinguished:**

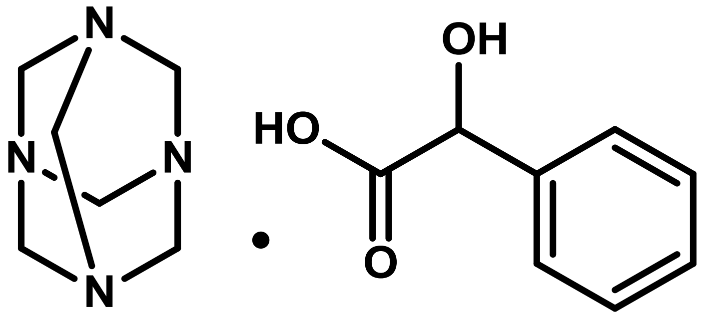
1. ***Molecular Addition***
2. ***Molecular Replication***
3. ***Molecular Hybridization***

2-Molecular association (Conjunction)

- **Molecular Addition:-**

✓ **It means association of different moieties through weak forces, such as**

- ➢ **Electostatic attraction.**
- ➢ **Hydrogen bonding e.g. Hexamine mandelate**
  - ✓ **Used for the treatment of urinary tract infection: hexamine decomposes at an acid pH to formaldehyde and ammonia, and the formaldehyde is bactericidal; the mandelic acid adds to this effect.**
  - ✓ **Urinary acidity is typically ensured by co-administering vitamin C (ascorbic acid) or ammonium chloride.**



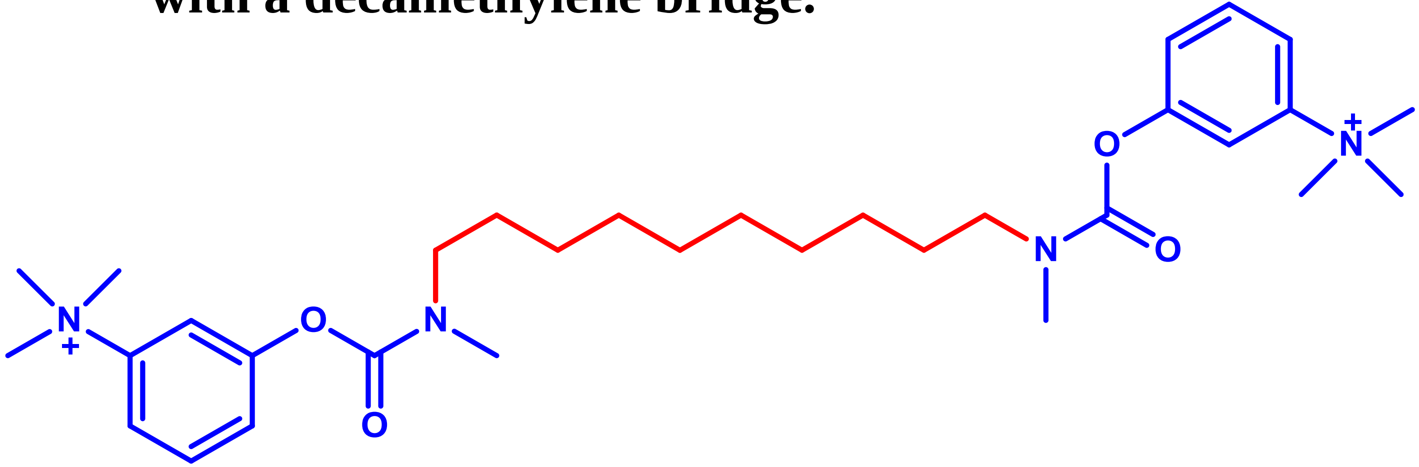
2-Molecular association (Conjunction)

- **Molecular Replication:-**

Association of <u>identical</u> moieties through <u>covalent bond</u> formation. (duplication or triplication).

Demecarium a parasympathomimetic that acts as an acetylcholinesterase inhibitor used to reduce elevated intraocular pressure associated with primary glaucoma in animals.

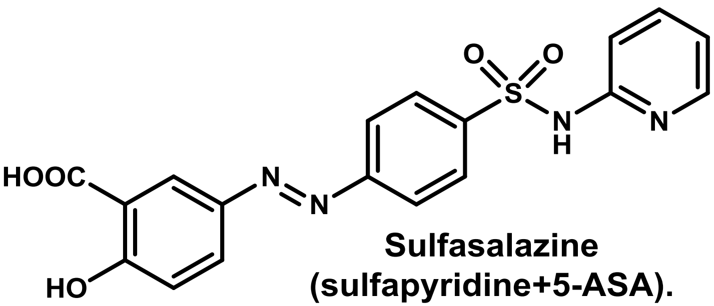
It is association of two molecules of neostigmine through covalent bonds with a decamethylene bridge.



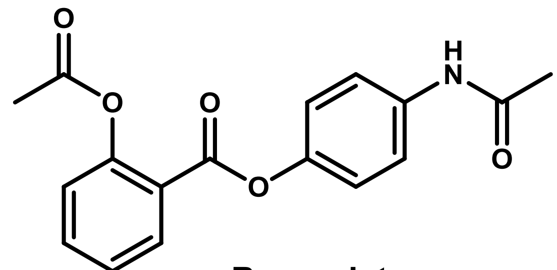
2-Molecular association (Conjunction)

- **Molecular Hybridization:-**

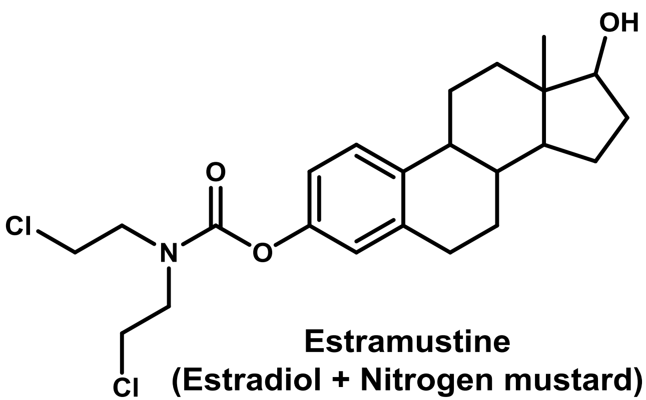
  Association of <u>different</u> or mixed moieties through <u>covalent-bond</u> formation.



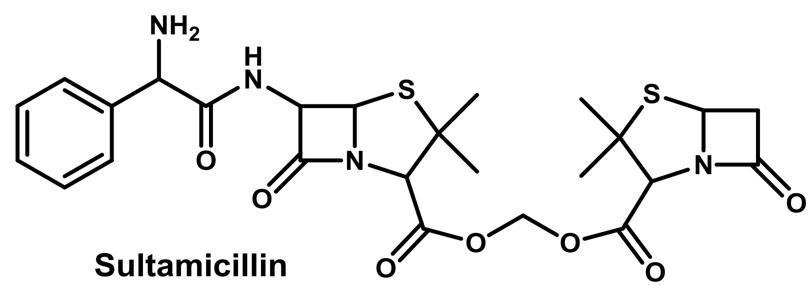
Sulfasalazine
(sulfapyridine+5-ASA).



Benorylate
(aspirin + paracetamol)



Estramustine
(Estradiol + Nitrogen mustard)



Sultamicillin
(Ampicillin + Sulbactam)

3- Skeletal Variations

Molecular modification of a lead compound through variation in the skeleton of the molecule, Why?

- **Changes may affect on the *physicochemical and pharmacokinetic properties* (liposolubility, ionization, electron distribution, stereochemistry, absorption, transport, excretion, metabolism)**
- **Changes may *improve the interaction between the drug and its target.* (Drug-Receptor interaction).**

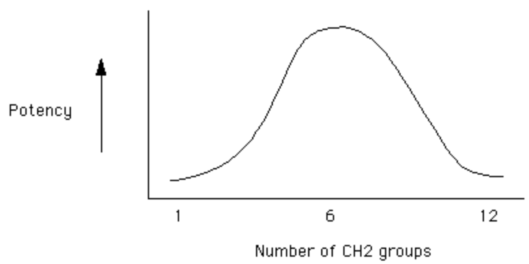
Molecular modification of a lead compound through variation in the skeleton of the molecule, How?

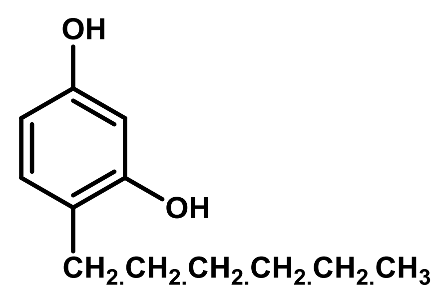
1. **Formation of Lower or Higher Homologs**
2. **Chain branching**
3. **Variation of substituents including bulky substituents.**
4. **Extension of the structure**
5. **Isosteric substitution**
6. **Ring-Chain transformation**
7. **Aromatic substitution: Design of aromatic ring position isomers.**
8. **Ring Variations (Ring expansion or contraction, Ring equivalence, Ring fusions)**
9. **Introduction of double bonds and Formation of rigid analogues.**

3.1- Formation of Lower or Higher Homologs

1. Alkane and polymethylene series of homologs can easily be formed, but ***it is not possible to establish rigid rules for the pharmacological properties of homologous compounds.***

- However, in the alkane and polymethylene series, some general types of change were noticed.
  - Activity increases regularly ***until a maximum is reached***, higher members being almost or entirely inactive.
  - An increase in the number of carbons in a chain may significantly increase the ***lipophilic character*** of the molecule and change the partition coefficient.





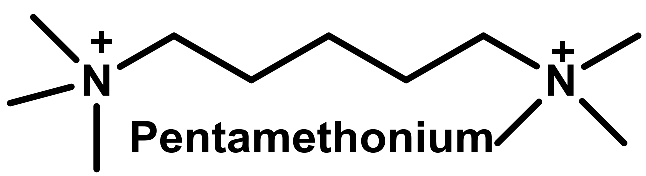
Phenols and Alcohols as anti-infective agents:
Relationship of potency to the number of methylene group (Homologation)

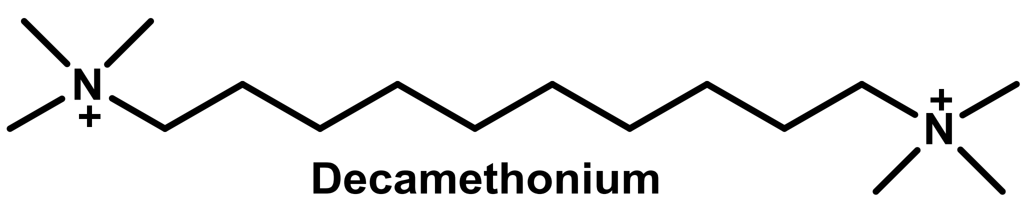
3.1- Formation of Lower or Higher Homologs

2. **Activity <u>changes:-</u> lower members having one type and higher members having a different type of predominant action.**

<u>Pentamethonium</u>, in which *5 methylene groups* separate two cationic trimethylammonium heads, is a ganglionic blocker.

<u>Decamethonium</u> is a depolarizing muscle relaxant or neuromuscular blocking agent used in anesthesia to induce paralysis.





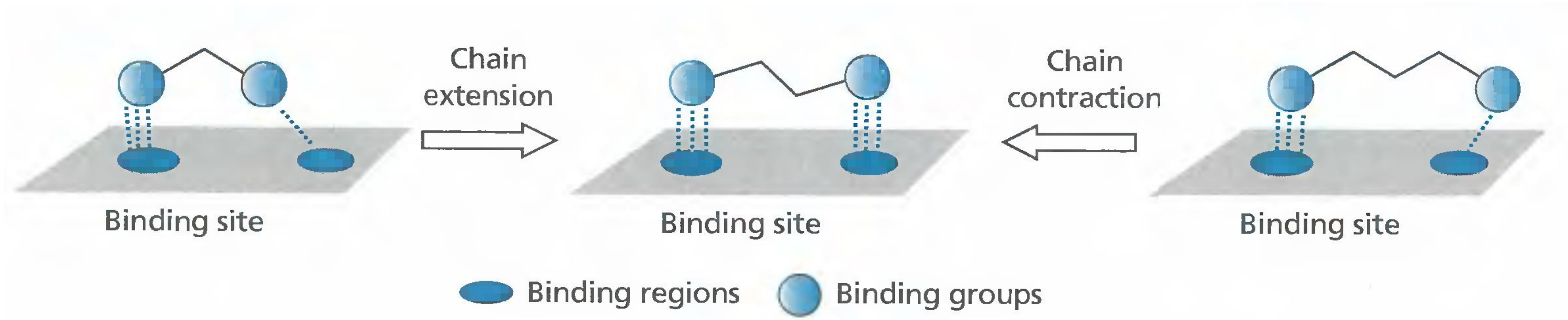
3.1- Formation of Lower or Higher Homologs

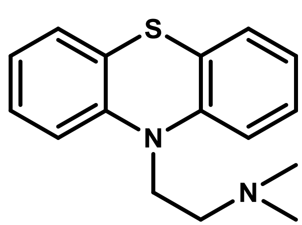
3. **Shortening or lengthening the chain between 2 important binding groups.**

Chain length is very important to drug-receptor interaction

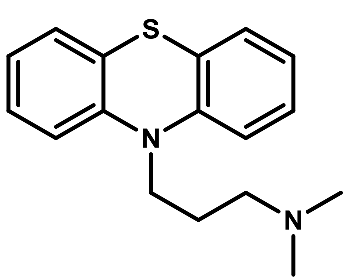
- ✓ **Homologation played an important role in developing antipsychotics from antihistaminics.**

Binding with different receptors





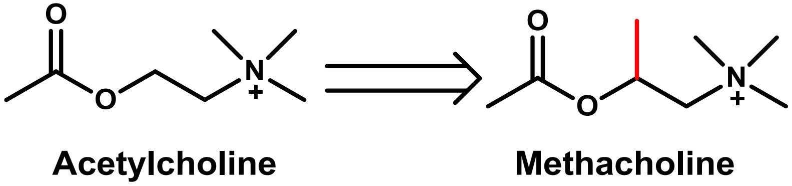
Promethazine
(antihistaminic with strong sedative and weak antipsychotic effects)



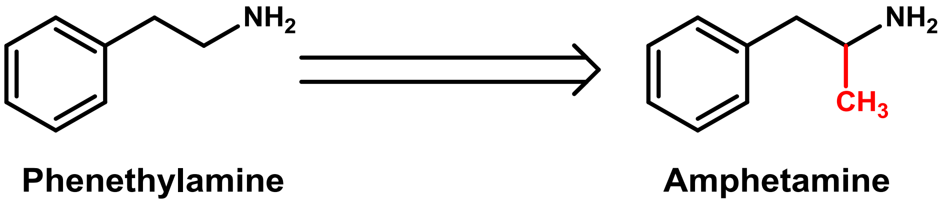
Promazine
(antipsychotic, used to treat schizophrenia)

3.2- Chain branching

- Addition or alteration of chain branches may affect the liposolubility, stereochemistry and/or the complimentarity with the receptor or with the catalytic surface of a metabolizing enzyme.
- e.g. β-methyl group in methacholine:-
  - Retards the hydrolytic effect of acetylcholinesterase enzyme → increases the duration of action. Also creates chiral carbon.



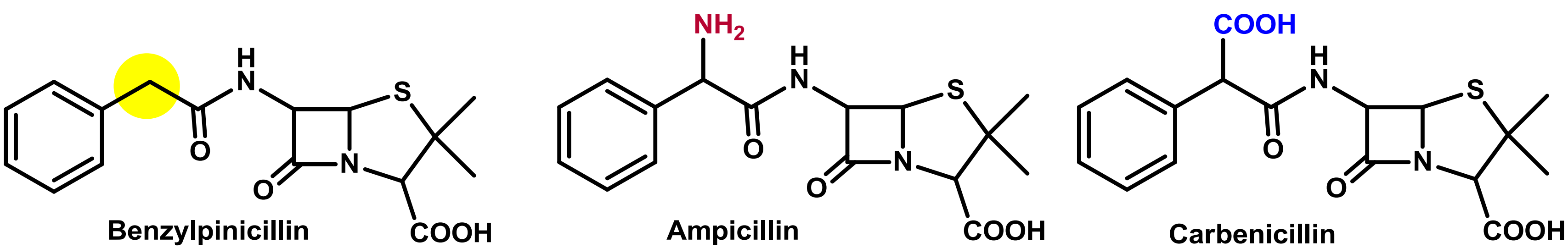
- Compounds with phenethylamine structure are good substrates for MAO enzymes.
  - Introduction of a methyl group at α-position makes the new compound a poor substrate for the enzyme (e.g. Amphetamine).



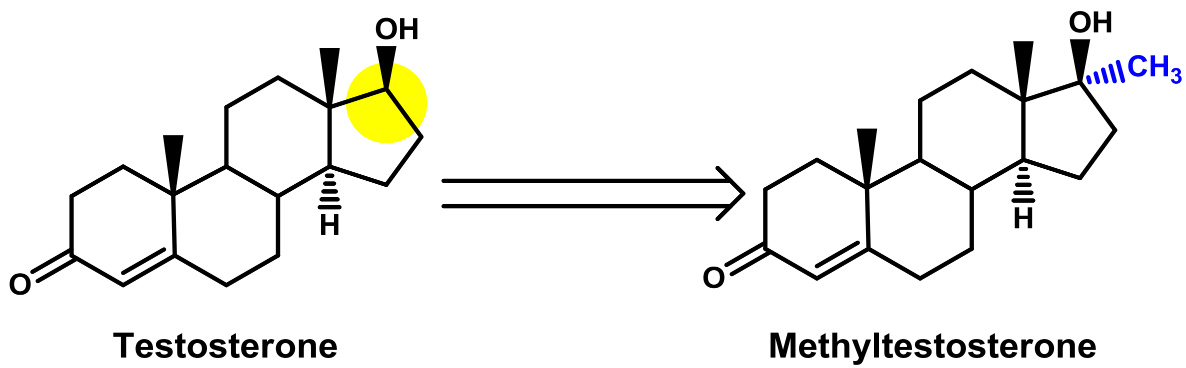
3.3- Variation of substituents

- **Introduction of a substituent will have an effect on: Hydrophobic, Electronic, Steric and Obstructive (Halogens) properties**

  Ex.1: Addition of a polar group at the α-position in benzylpencillin→ polar compounds that penetrate the outer layer of the Gram-negative bacteria, so *ampicillin and carbenicillin are active against Gram-negative bacteria.*



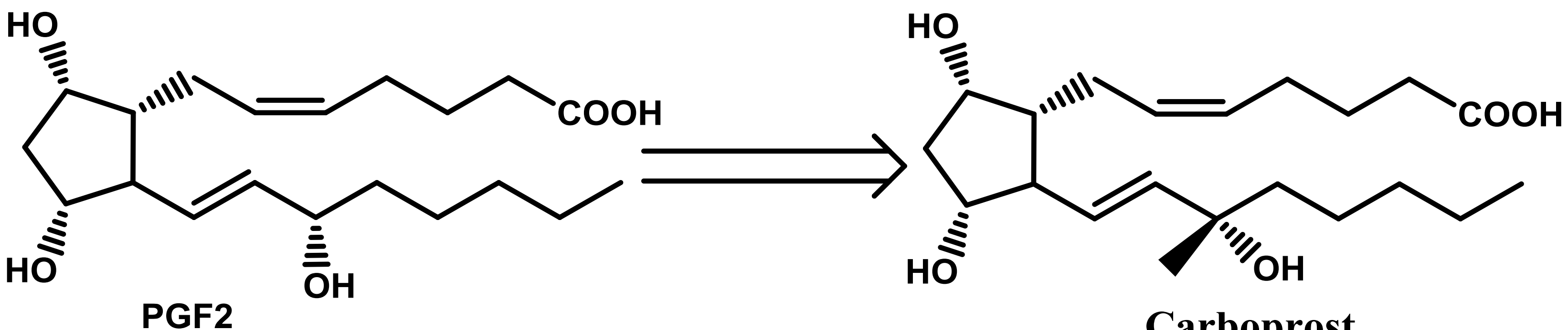
Ex.2: Methyltestosterone: Effect of substituents →Retardation of Metabolism



3.3- Variation of substituents

Ex.3: Carboprost

- ✓ **derivatives of PGF2**
- ✓ **has a very high *uterotropic activity and is used to induce abortion.***
- ✓ **The presence of the 15-methyl group → inhibition of the dehydrogenase enzyme that inactivates PGs at the 15-OH.**

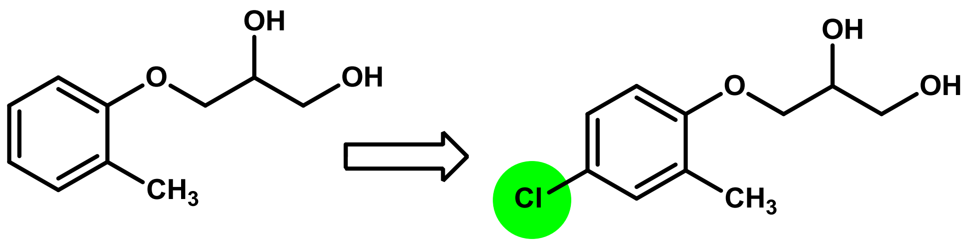


Carboprost

3.3- Variation of substituents

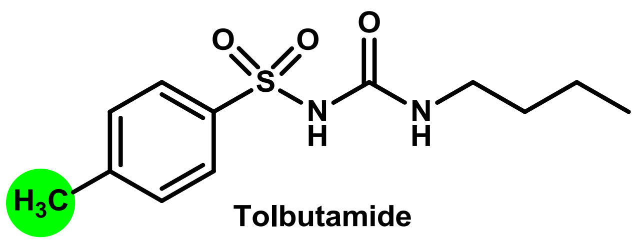
- It is known that the process of detoxification of aromatic rings is hydroxylation in <u>para position </u>and afterward are conjugated with glucuronic acid.

Halogenation in the *p*-position of aromatic rings of some drugs (e.g. mephenesin: a centrally acting muscle relaxant used as an antidote for strychnine poisoning.) in order to prevent hydroxylation so decrease the metabolic rate.

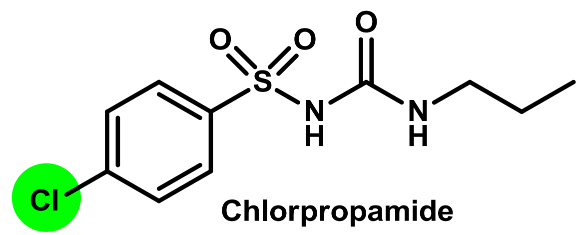


Mephenesin

In chlorpropamide, the chlorine atom replaced a methyl group of the parent tolbutamide that was very subjected to oxidation so increase the duration of action.



Tolbutamide



Chlorpropamide

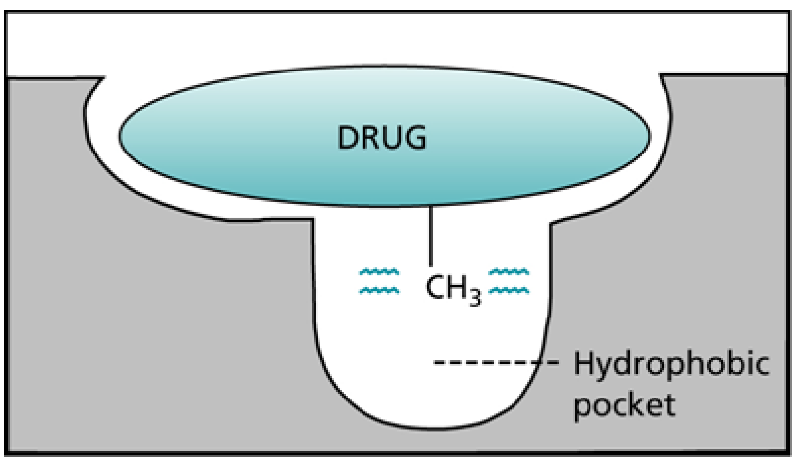
3.3- Effect of substituents

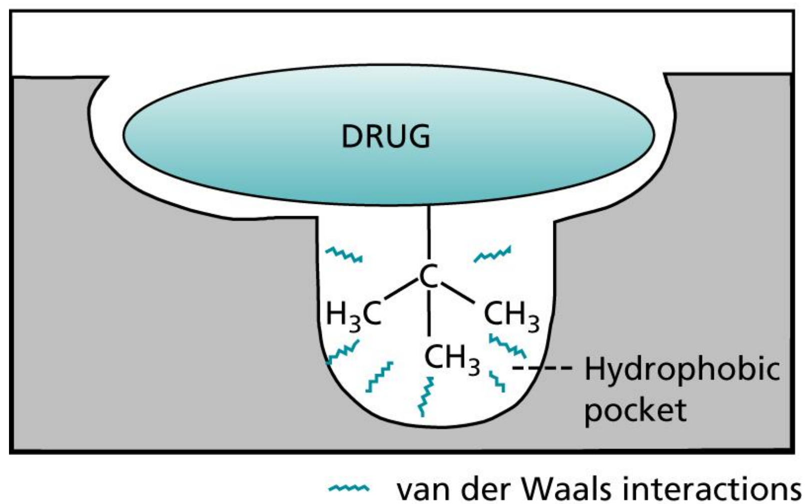
- **Alkyl substitution**

  Such as methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or tert. butyl are often used to investigate the effect of chain length and bulk on binding.

  If these group interact with a hydrophobic pocket present in the target receptor, then increasing length and/or bulk of the alkyl chain will increase the binding interaction.

  Variation of alkyl chain to fill a hydrophobic pocket which increase the binding interaction with the target receptor.





3.3- Variation of substituents

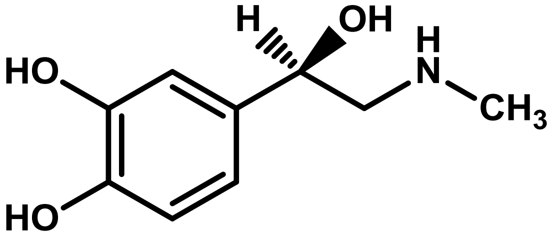
Alkyl substitution

Use of larger alkyl group to confer selectivity on a drug, in case of drugs which interact with two different receptors.

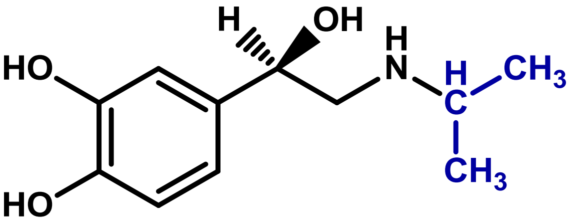
- **Adrenaline is a direct <u>non selective</u> adrenergic agonist (α and β-receptors)**

  Isoproterenol is a synthetic catecholamine, with potent β-adrenergic agonist activity, but no effect on α-receptors

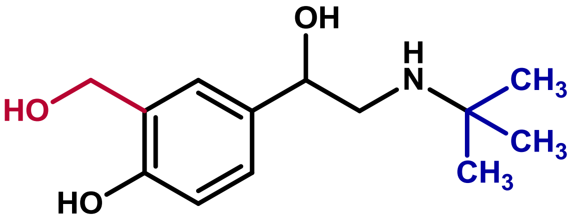
  - **Albuterol (Salbutamol) : resist metabolism by COMT**



Adrenaline



Isoprenaline



Albuterol

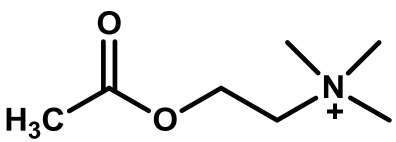
3.3- Variation of substituents

- **Addition, Removal, or Replacement of Bulky Substituents**

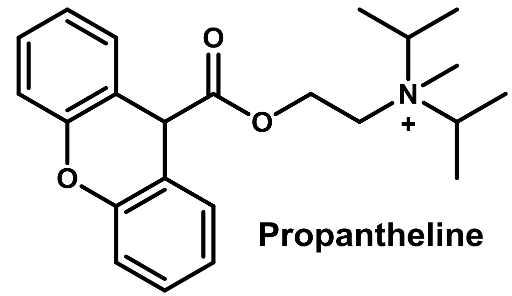
  In many cases, higher members are <u>antagonists</u> of the pharmacological effect of lower members. This is illustrated by "addition of bulky groups".

  In many cases, the difference between agonists and antagonists is the presence of nonpolar bulky groups in antagonists

  e.g. <u>Propantheline versus Acetylcholine</u>

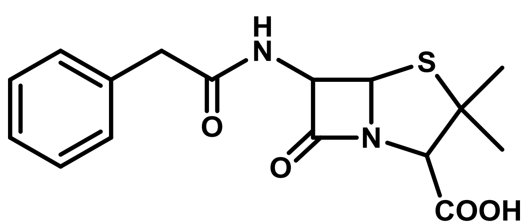


Acetylcholine

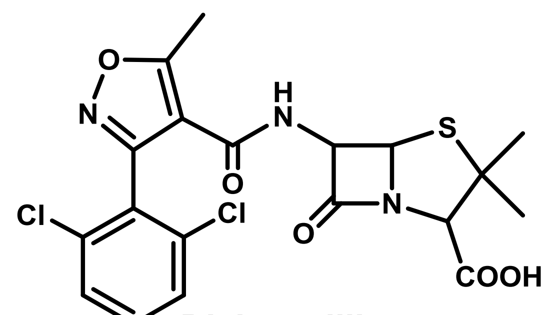


Propantheline

- **e.g. <u>β-lactamase-resistant penicillin</u>: Bulky groups introduced near this ring prevent the approach of the β-lactamase enzyme by <u>steric hindrance</u>, thus making the penicillins formed resistant. (e.g. Dicloxacillin).**



Benzylpenicillin



Dicloxacillin

3.3- Variation of substituents

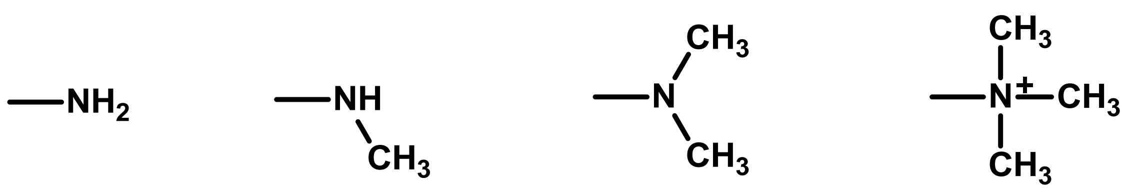
- N-Alkylation

  Primary through quaternary amines

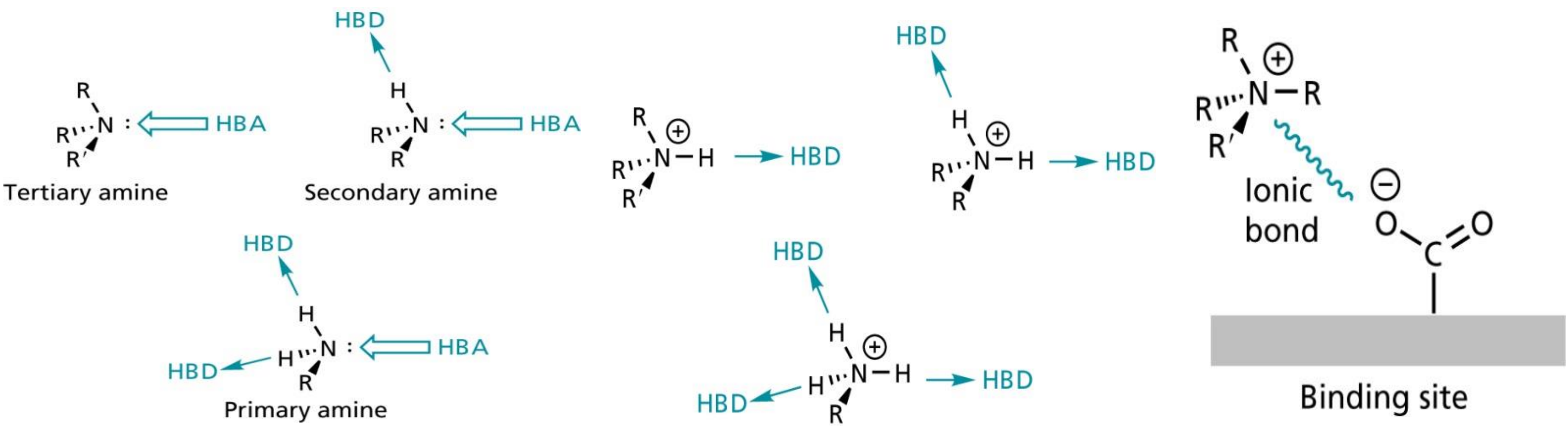
  ✓ Which one is more lipophilic?

  Which one has retarded metabolism?

  ❖ Which one is devoid of the central activity?

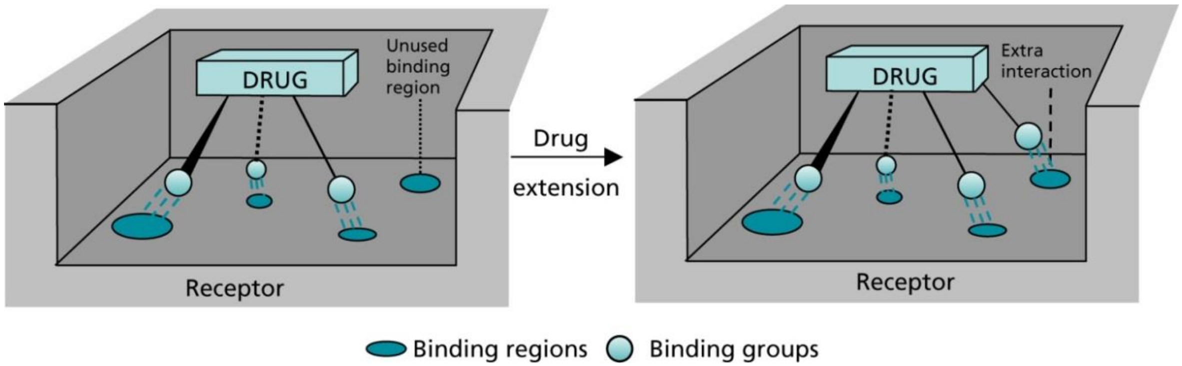


Pri. amine | Sec. amine | Ter. amine | Quat. amine

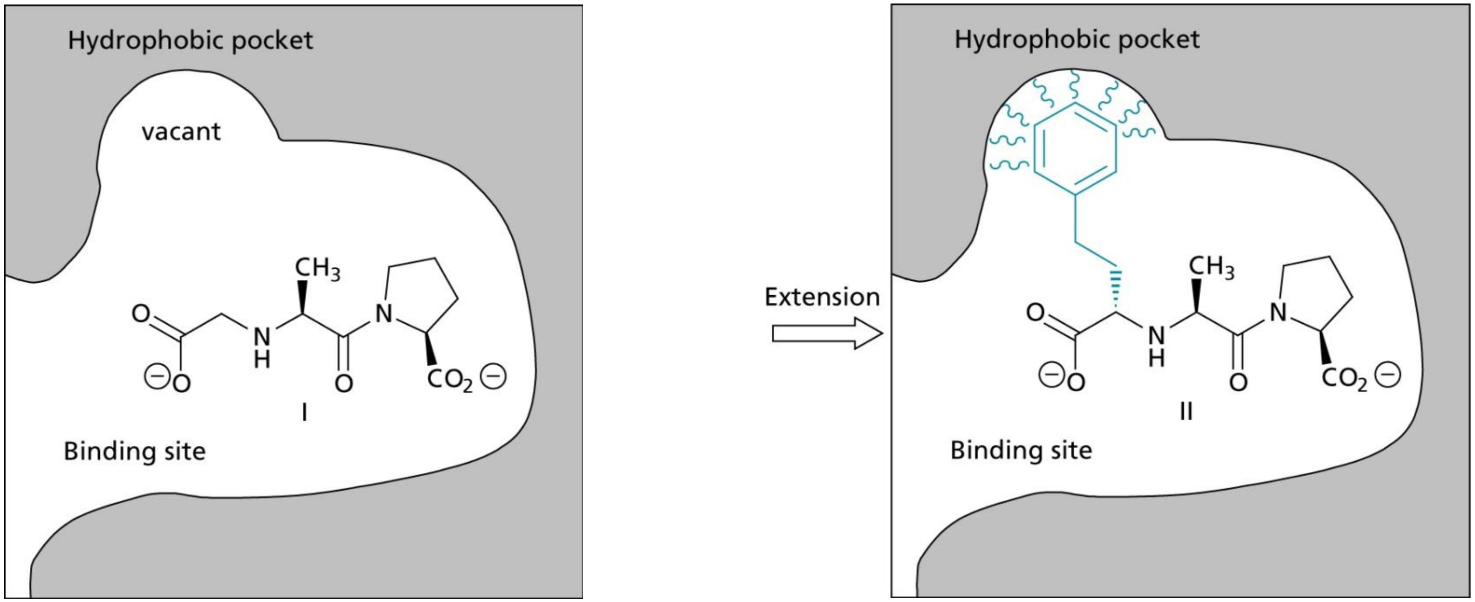


3.4- Extension of the structure

- Addition of another functional group to the lead compound for extra binding target interaction.



Ex. Adding a phenylethyl group to (ACE inhibitor) resulting in better inhibition via binding to an extra hydrophobic pocket in the enzyme.



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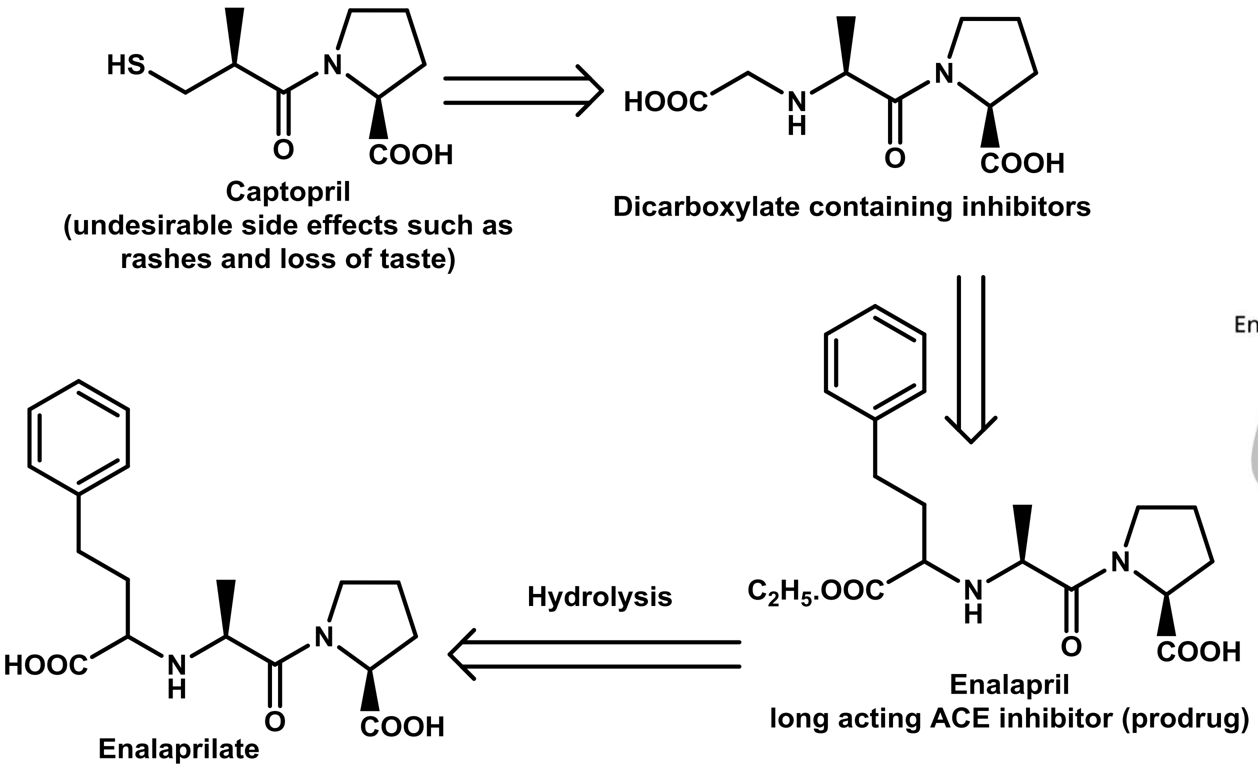
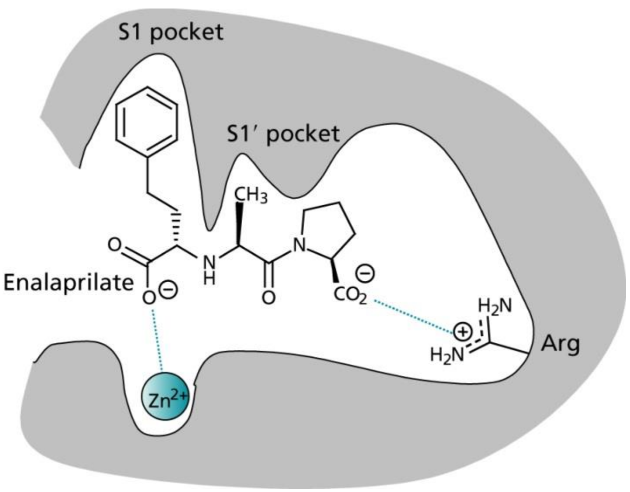
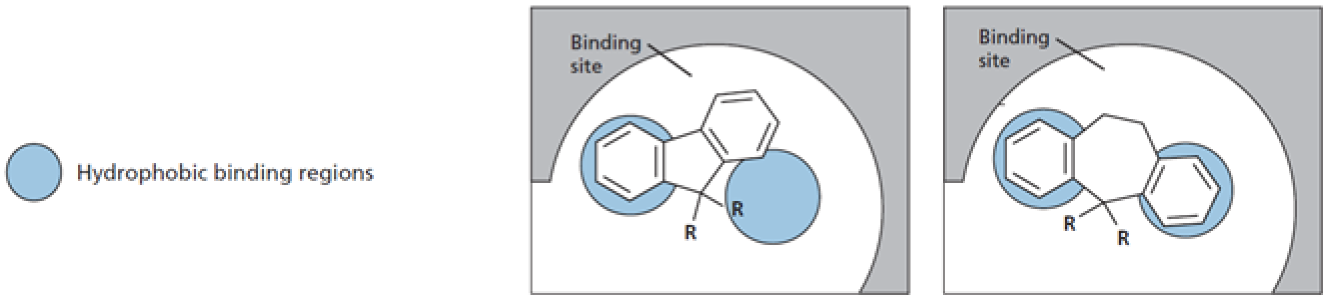




3.5- Ring variation

Ring expansion/contraction

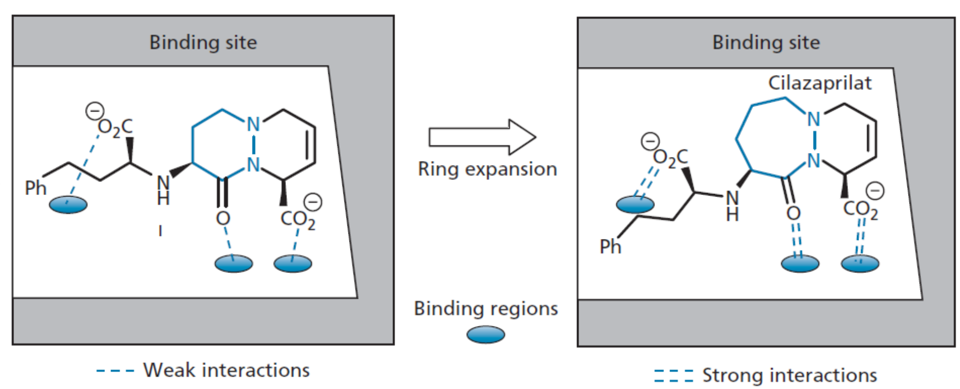
- Expanding or contracting a ring may put other rings in different positions relative to each other, and may lead to better interactions with specific regions in the binding site



6,5,6 ring system has a poor interaction with both hydrophobic regions

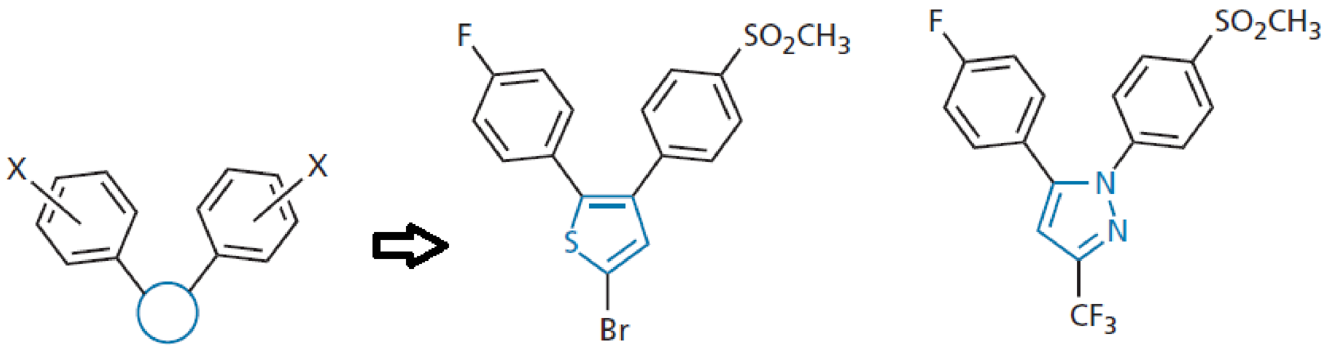
6,7,6 ring system has the optimum interaction with both hydrophobic regions

- Varying the size of a ring can also bring substituents into a good position for binding.
- Example: Cilazaprilat



3.5- Ring variation

- **Ring change**
  - **Replace the original ring with a range of other heteroaromatic rings of different ring size and heteroatom positions.**
- **Purposes:**
  - **Avoiding patent restrictions <u>(‘me too’ drugs).</u>**
  - **Different pharmaceutical companies have varied the central ring to produce a range of active compounds.**
  - **Example: NSAIDs**



General structure for NSAIDs

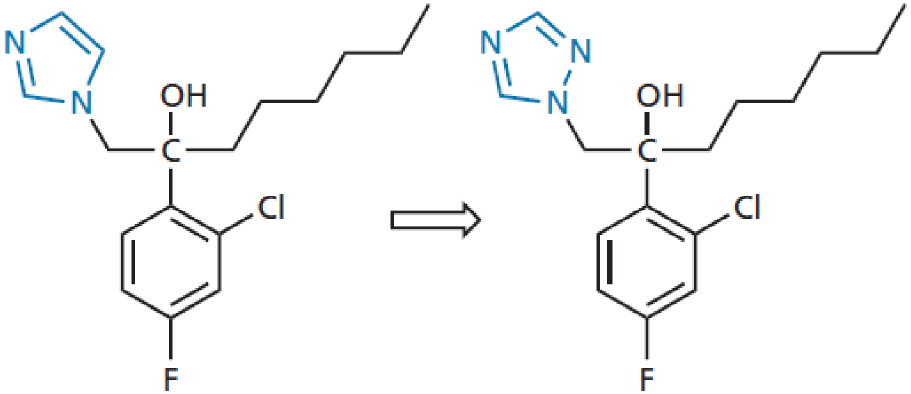
DuP 697

SC 58125

3.5- Ring variation

- **Ring change**
- **Significant improvements in activity, as well as increased selectivity and reduced side eff ects (‘ me-better’drugs).**

- **Example: Antifungal compounds (Structure I & UK46245).**
- **Replacing the imidazole ring of structure (I) with a 1,2,4-triazole ring to give UK 46245 resulted in better selectivity against the fungal form of the enzyme.**

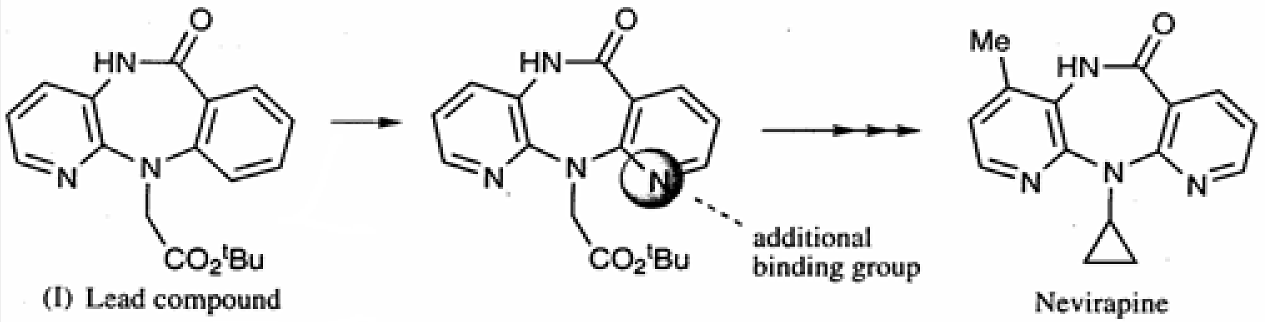


Structure I UK 46245

3.5- Ring variation

- **Ring change**
- ✓ **Introduces the possibility of an extra hydrogen bonding interaction with the binding site, if a suitable binding region be available.**

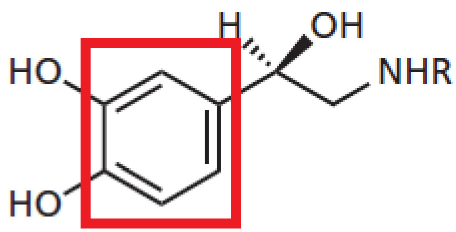
- **Example: (Development of Nevirapine).**
- **Structure I was the lead compound for novel antiviral agents. Replacing the aromatic ring with pyridine resulted in an additional binding interaction with the target enzyme.**
- **Further development led eventually to nevirapine.**



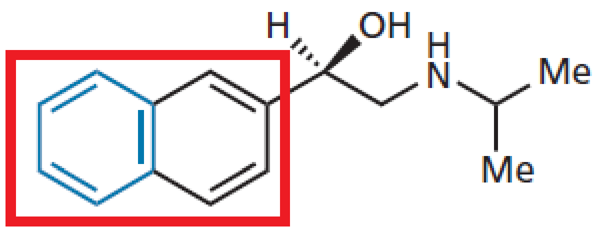
Development of nevirapine

3.6- Ring fusion

- **Extending a ring by ring fusion can result in increased interactions or increased selectivity.**
- **Example: Development of the selective β-blockers**
- **The replacement of the aromatic ring in adrenaline with a naphthalene (pronethalol).**
- ***The β-receptor has a larger van der Waals binding area for the aromatic system than the α-receptor, and can interact more strongly with pronethalol than with adrenaline.***
- ***Another possible explanation is that the naphthalene ring system is sterically too big for the α-receptor, but is just right for β-receptor.***



R = Me Adrenaline
R = H Noradrenaline



Pronethalol